IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s)	:	Leneau and Skelly
Serial No.	:	09/586,510
Filing Date	:	June 2, 2000
Title	:	METHODS OF MAKING AND USING (Ig) IMMUNOGLOBULIN COMPOSITIONS
Group/Art Unit	:	1644
Examiner	:	R.B. Schwadron
Confirmation No.	:	7522
Docket No.	:	503775.008

DECLARATION III OF HOWARD ERICKSON

I, Howard Erickson, do hereby declare and state as follows:

1. I have a Doctorate of Veterinary Medicine from Kansas State University (1959) and a Ph.D. from Iowa State University (1966).
2. I am a Professor of Physiology at the Kansas State University College of Veterinary Medicine, where I have been employed as a Professor of Physiology in the Department of Anatomy & Physiology since 1981. In 2001 I was named the Roy Walter Upham Professor of Veterinary Medicine.
3. In 1987 I spent a sabbatical leave at the Equine Research Station, Animal Health Trust, Newmarket, England and the College of Veterinary Medicine, Swedish University of Agricultural Sciences, Uppsala, Sweden.
4. I have received numerous honors and achievements in my field, including the Bayer Excellence in Equine Research Award (2000). I was elected a Fellow of the American Association for the Advancement of Science in 1976 and a member of Phi Kappa Phi in 1985 which recognizes superior scholarship in all academic disciplines. I became a member of the Phi Zeta, Honor Society of Veterinary Medicine in 1966.
5. I have worked in the field of Equine Sports Medicine and Exercise Physiology since 1982. I have specialized in exercise-induced pulmonary hemorrhage (EIPH), comparative exercise physiology, and cardiopulmonary physiology. I

began to study exercise physiology in 1966 at the United States Air Force School of Aerospace Medicine.

6. I have reviewed and am familiar with the subject matter disclosed in the above referenced patent application.
7. William G. Skelly, one of the inventors of the above referenced patent application, disclosed to me the concept of using immunoglobulin (Ig) as a treatment for stress induced respiratory disorders, including EIPH. After such disclosure, I began to research the use of Ig compositions as a treatment for EIPH. I have statistically significant, documented evidence that the administration of Ig can be used as an effective treatment for a form of "stress induced respiratory disorder," manifested as EIPH.
8. Under my direction and control, Seramune Equine IgG™ was used to treat adult thoroughbred horses diagnosed with EIPH. Seramune Equine IgG™ is an equine serum concentrate that contains IgG as well as other immunoglobulins. Prior to treatment, all of the horses were confirmed "bleeders". Evidence of this was measured by bronchoalveolar lavage (BAL) prior to treatment with the Ig composition.
9. Seramune Equine IgG™ was administered by sterile technique at a dosage of 20 cc intratracheally and 10 cc intravenously for 5 injections, and repeated at 24 hour intervals. This was followed by weekly booster injections using the same dose and route of administration. If the horse was performing that week (maximal effort exercise test), the weekly booster was given 24 hours before the performance. The horses were not treated with anything else before exercising. Initial preliminary efficacy studies utilized a pre-treatment baseline for each horse as a control. Use of such a control is statistically valid, and in fact, improves the validity of results over results obtained from comparing different animals. However, in the interest of scientific validity, we have proposed to complete control runs using saline in place of Seramune Equine IgG™, but using the same volumes and procedures of administration.
10. Objective evidence of the reduction of EIPH after treatment with the Ig composition included:

53% reduction in RBC's/ml in the BAL fluid

32% reduction in WBC's/ml in the BAL fluid

These numbers have been updated from my declaration dated October 7, 2002 to include additional data and final statistical analysis. This evidence establishes that the administration of Ig is an effective treatment for EIPH.

11. In view of our successful use of Seramune Equine IgG™ for treating EIPH and Ragland's use of Seramune to treat respiratory disease, I believe that IgG compositions would likely be useful in treating other stress induced respiratory disorders in the horse.
12. In view of the successful use of Seramune Equine IgG™ for treating EIPH in horses, I believe that other species-specific IgG compositions would likely be useful in treating EIPH and other stress induced respiratory disorders in other animals.
13. In view of the successful use of Seramune Equine IgG™ for treating EIPH in horses, I believe that other species-specific Ig compositions may be useful in treating EIPH and other stress induced respiratory disorders in horses and other animals.
14. It is my understanding that the reviewer of the above referenced patent application argued that the cause of EIPH involves stress failure of pulmonary capillaries from high pulmonary vascular pressures based on my paper published in the Equine Veterinary Journal in 1995.
15. However, research from our laboratory, as well as from that of other investigators, has shown that other factors such as the work of breathing and upper airway resistance result in large changes in extravascular pressures (i.e. Flair Equine Nasal Strip), as well as inflammatory airway disease (preliminary EIPH efficacy study at Kansas State University, studies by McKane et al. from Australia, Newton and Wood from Newmarket, and the 1995 Seramune study by Ragland) may contribute to EIPH and its severity in addition to elevations in pulmonary arterial pressures. The preliminary efficacy study discussed above showed a reduction in WBC counts/ml BAL fluid, which

may indicate a reduction in airway inflammation as well as bleeding. However, while the mechanism of action is unclear, it is also believed to be immune regulatory in origin based upon published literature and very preliminary work in progress in our laboratory

16. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application and any issued patent resulting therefrom.

14 Oct 2003 Howard H. Erickson

Date Howard H. Erickson

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DECLARATION II OF WILLIAM G. SKELLY

I, William G. Skelly, declare as follows:

1. I am the sole inventor of the subject matter claimed in the above-identified patent application, including, the method of administering an immunoglobulin (Ig) composition to horses suffering from equine respiratory infection.

2. I am president of Central Biomedia, Inc., assignee of the above-identified patent application. Sera, Inc. is a wholly owned subsidiary of Central Biomedia, Inc. Sera, Inc. sells Ig compositions under the trademark SERAMUNE (R).

3. I have reviewed the article entitled "Passive Immunotherapy of Equine Respiratory Disease: Treatment of Acutely Ill Horses with Equine Immunoglobulins," The Equine Athlete, Vol. 8, No. 6 (1995), authored by Ragland, McCullough and Wilkey.

4. I am the inventor of the method of administering an Ig composition to horses suffering from equine respiratory infections disclosed in the above-referenced article. The authors of the above-reference article derived their knowledge of treatment from me. Specifically, I disclosed to Henry Leneau and other employees of Sera, Inc. the concept of using Ig compositions for treating stress-induced respiratory disorders, including respiratory infections of horses. On behalf of Sera, Inc. and myself, Mr. Leneau approached the authors of the above-referenced article to request they conduct the experiments described in the article. The authors conducted the experiments described in the article on behalf of Sera, Inc. and myself, using standard techniques. Sera, Inc. provided the material used in the experiments described in the article (see page 2, col. 1).

5. I confirm that none of the authors of the publication are inventors of the subject matter of the above identified invention.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: October 10, 2003 By: W. G. Skelly